Differential Association of Microvascular Attributions With Cardiovascular Disease in Patients With Long Duration of Type 1 Diabetes

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Diabetes Care 2018;41:815–822 | https://doi.org/10.2337/dc17-2250

OBJECTIVE

Independent association of chronic kidney disease (CKD) and proliferative diabetic retinopathy (PDR) with cardiovascular disease (CVD) has not been established. In the Joslin 50-Year Medalist study, characterizing individuals with type 1 diabetes for 50 years or more, we examined the associations of CKD and PDR with CVD, which was validated by another cohort with type 1 diabetes from Finland.

RESEARCH DESIGN AND METHODS

This cross-sectional study characterized U.S. residents (*n* = 762) with type 1 diabetes of 50 years or longer (Medalists) at a single site by questionnaire, clinical, ophthalmic, and laboratory studies. A replication cohort (*n* = 675) from the longitudinal Finnish Diabetic Nephropathy Study (FinnDiane) was used. CKD and PDR were defined as estimated glomerular filtration rate <45 mL/min/1.73 m^2 (CKD stage 3b) and according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, respectively. CVD was based on questionnaires and/or hospital discharge registers. Associations of CVD status with CKD and PDR were analyzed by multivariable logistic regression.

RESULTS

CVD prevalence in the Medalists with CKD and without PDR (+CKD/−PDR) (*n* = 30) and CVD prevalence in the −CKD/+PDR group (*n* = 339) were half the prevalence in the +CKD/+PDR group (*n* = 66) (34.5% and 42.8% vs. 68.2%, *P* = 0.002). PDR status was independently associated with CVD (odds ratio 0.21 [95% CI 0.08–0.58], *P* = 0.003) in patients with CKD. Among the Finnish cohort, a trend toward a lower prevalence of CVD in the +CKD/−PDR group (*n* = 21) compared with the +CKD/+PDR group (*n* = 170) (19.1% vs. 37.1%, *P* = 0.10) was also observed.

CONCLUSIONS

Absence of PDR in people with type 1 diabetes and CKD was associated with a decreased prevalence of CVD, suggesting that common protective factors for PDR and CVD may exist.

Hyperglycemia, diabetes duration, dyslipidemia, hypertension, and insulin resistance are established risk factors for both microvascular complications and cardiovascular disease (CVD) in patients with diabetes (1–4). Further, the presence of chronic kidney disease (CKD) in people with type 1 diabetes increases CVD risk by almost twofold (5).

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Received 26 October 2017 and accepted 30 December 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2250/-/DC1.

Since proliferative diabetic retinopathy (PDR) occurs frequently with CKD, it has been difficult to discern the independent contribution of CKD and PDR to CVD in type 1 diabetes owing to the limited number of people with CKD but without PDR (6).

Several studies in type 1 and type 2 diabetes have associated diabetic retinopathy (DR) with increased risks of CVD- and all-cause mortality (7–9). Davis et al. (9) reported that patients diagnosed with insulin-dependent diabetes had a 55% decrease in survival among those with PDR compared with those without the disease. Similar declines in survival in patients with type 1 diabetes and PDR were observed in the EURODIAB study and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (8,10). However, the independent contribution of PDR to CVD is unclear owing to the presence of albuminuria and CKD (8,10).

The frequent association of PDR with diabetic kidney disease is well established by multiple studies such as the Finnish Diabetic Nephropathy Study (FinnDiane) and WESDR (5,11). The co-occurrence of CKD and PDR is not surprising, since chronic hyperglycemia is the major contributor to diabetic microvascular complications. Therefore, an intriguing question arises as to whether the presence of PDR affects CVD prevalence in patients with type 1 diabetes with or without CKD.

This question can potentially be answered by the Joslin 50-Year Medalist study, which characterized individuals with 50 or more years of type 1 diabetes and has reported a low prevalence of CKD and PDR but with prevalence of CVD similar to that in people with type 2 diabetes (12). The availability of a significant number of Medalists with CKD, yet without PDR, provides a unique opportunity to characterize the independent contribution of CKD or PDR to CVD. Therefore, the objective of this study was to investigate the independent associations of diabetic retinal and renal disease with CVD in patients with type 1 diabetes. In addition, we used the FinnDiane cohort, a large type 1 diabetes cohort of shorter duration, for replication.

RESEARCH DESIGN AND METHODS

Medalist Patients

The Medalist study took place between 2004 and 2015 and enrolled >1,000 patients from all 50 U.S. states. All individuals had documented at least 50 years of insulin treatment for type 1 diabetes and were examined at the Joslin Diabetes Center. Only patients with comprehensive data on micro- and macrovascular complications (n = 762) were included in the analysis (13). Participants completed medical history questionnaires and received a physical and an ophthalmic examination at the Joslin Diabetes Center. The study protocol was approved by the Joslin Committee on Human Subjects. Written informed consent was obtained from each patient.

HbA_{1c} was assessed by high-performance liquid chromatography (G7 and 2.2 analyzers; Tosoh, Tokyo, Japan). Lipid profiles, serum albumin, and creatinine were assessed by standardized assays at the Joslin clinical laboratories. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate (eGFR) (14). C-reactive protein (CRP) was measured by particle-enhanced immunonephelometry (BN ProSpec analyzer; Dade Behring, Deerfield, IL), and serum C-peptide was measured at the Northwest Lipid Research Laboratory of the University of Washington (15). DRB1 and DQB1 genotyping was determined by linear arrays of immobilized sequence-specific oligonucleotides as previously described (16). Autoantibodies (IA2 and GAD65) were assayed at the Barbara Davis laboratory at the University of Colorado (17).

Kidneys were obtained postmortem from Medalists who had consented and shipped on ice and saline gauze within 10 h of death, coordinated by the National Disease Research Interchange. Histological evaluation was performed by experienced renal pathologists (P.S.A. and I.E.S.) blinded to clinical data, using standard renal pathology techniques (including light microscopy, immunofluorescence, and electron microscopy). Each case was graded according to the Renal Pathology Society pathologic classification of diabetic nephropathy (18).

CKD was defined as eGFR <45 mL/min/1.73 m^2 equaling stage 3b CKD. Seven standard field stereoscopic fundus photographs were graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol to classify DR, read by two trained reviewers, and adjudicated as needed (19). PDR was defined as a score >53. Diabetic peripheral neuropathy was based on the Michigan Neuropathy Screening Instrument with physical examination. A score ≥2 was considered positive for peripheral neuropathy (20). History of coronary artery disease, angina, or heart attack or a prior cardiac/leg angioplasty or bypass graft surgery was determined by validated questionnaires and verified by the physician/research nurse at the research center. Moreover, a history of coronary artery disease was validated by an electrocardiogram at visit (Q-waves and ST- or T-wave changes) (21).

FinnDiane Patients

The FinnDiane cohort comprises individuals with type 1 diabetes defined as an onset of diabetes before the age of 40 years and insulin treatment initiated within 1 year of diagnosis (22). Patients were recruited from 93 hospitals or health care centers across Finland in 1997 and followed for a median of 13 years. For comparison with the Medalist study, only those with data on retinopathy scored using the ETDRS scale and 25 years or more of type 1 diabetes duration were included in this analysis (n = 675). The FinnDiane protocol was approved by the ethics committee of the Helsinki and Uusimaa Hospital District and by each study center in accordance with the Declaration of Helsinki with individual written consent.

Information on medication, cardiovascular status, and diabetes complications was collected by standardized questionnaires, completed by the attending physician, and verified by the medical record. HbA_{1c}, lipid profiles, albumin, and creatinine were determined by standardized assays at each center (22). C-peptide and CRP were measured by commercial kits (Human C-Peptide RIA Kit; Linco Research, St. Charles, MO) and immunochemical methodology (Orion Diagnostica, Espoo, Finland), respectively.

Renal disease was defined as an eGFR <45 mL/min/1.73 m^2 (CKD stage 3b) using the CKD-EPI formula (14), and PDR was defined as a score ≥60 on the ETDRS scale. CVD events, obtained from medical files and the Finnish Hospital Discharge Register, were defined by history of bypass grafting surgery or angioplasty, stroke, or a peripheral artery procedure (bypass grafting surgery, angioplasty, or amputation) (22).

Statistical Analysis

All variables were visually inspected and analyzed for distribution to determine appropriate statistical methods for analysis. All data are presented as median with interquartile range (IQR) or percentage. Differences between groups were analyzed with Student *t* test, ANOVA, or Kruskal-Wallis test as appropriate. Categorical variables were analyzed using the Pearson χ^2 test. A *P* value of $\leq$0.05 was considered significant. Multivariable logistic regression analysis was performed to determine the influence of clinical group on CVD prevalence, adjusted for possible confounding. For construction of these models, candidate variables (Table 1), particularly those that differed among groups or with known associations with outcomes or complications of diabetes, were added to the model in a systematic fashion and remained if they were significantly associated with CVD ($P < 0.05$) or if their inclusion in the model changed the estimated coefficient for another term by 15% or more (23). Possible interactions of each of these variables with clinical group were tested in the model as multiplicative terms. Analyses were performed with Stata (College Station, TX) and SAS, version 9.4 (Cary, NC).

RESULTS

Medalist Patients

Medalists with complete data on micro- and macrovascular complications included in this study (*n* = 762) did not vary from the overall cohort (*n* = 952) for relevant traits. The clinical profile of Medalists in the analysis set showed that 55% were female, with median age 65 years (IQR 60, 70) and diabetes duration of 53 years (51, 56), with a prevalence of CKD, PDR, and CVD of 12.9%, 53.3%, and 38.9%, respectively (Supplementary Table 1).

Characteristics of Medalist Patients Grouped by CKD, PDR, and CVD

For examination of factors related to the distribution of microvascular and macrovascular complications, the Medalist cohort was divided and analyzed by the following four categories (as shown in Table 1): CKD and no PDR (+CKD/−PDR) (*n* = 30), no CKD and no PDR (−CKD/−PDR) (*n* = 327), CKD and PDR (+CKD/+PDR) (*n* = 66), and no CKD and PDR (−CKD/+PDR) (*n* = 339).

Participants with +CKD/−PDR were significantly older at diagnosis of type 1 diabetes than the other groups. No differences in HbA_{1c} between the groups were found. As expected, eGFR was significantly lower and albumin-to-creatinine ratio (ACR) was higher in groups with

Table 1—Clinical characteristics of Medalists stratified by the presence of CKD and PDR

	+CKD/−PDR	−CKD/−PDR	+CKD/+PDR	−CKD/+PDR
N	30	327	66	339
Sex (male)	46.7	46.8	40.9	44.3
Age (years)	**73 (67, 77)***	**65 (61, 70)**	**65 (62, 71)**	**64 (60, 70)**
Age at diagnosis (years)	**15 (10, 21)***	**11 (6, 16)**	**10 (7, 14)**	**10 (6, 14)**
Duration (years)	54 (51, 63)	53 (51, 56)	54 (51, 58)	53 (51, 56)
Daily insulin dose (units/kg)	0.48 (0.31, 0.62)	0.42 (0.34, 0.52)	0.44 (0.33, 0.56)	0.43 (0.35, 0.54)
HbA_{1c} (%)	7.0 (6.4, 8.0)	7.1 (6.5, 7.6)	7.2 (6.4, 7.8)	7.2 (6.7, 7.7)
HbA_{1c} (mmol/mol)	53 (46, 64)	54 (48, 60)	55 (46, 62)	55 (50, 61)
Total cholesterol (mmol/L)	3.8 (3.4, 4.4)	4.1 (3.7, 4.7)	4.0 (3.4, 4.5)	4.0 (3.5, 4.7)
LDL cholesterol (mmol/L)	2.0 (1.5, 2.5)	2.0 (1.7, 2.4)	2.0 (1.6, 2.5)	2.0 (1.7, 2.3)
HDL cholesterol (mmol/L)	**1.4 (1.1, 1.8)***	**1.7 (1.4, 2.1)**	**1.4 (1.2, 1.7)**	**1.6 (1.3, 2.0)**
Triglycerides (mmol/L)	**0.8 (0.7, 1.2)***	**0.7 (0.6, 0.9)**	**1.0 (0.7, 1.2)**	**0.7 (0.6, 1.0)**
BMI (kg/m^2)	**25.5 (23.6, 28.3)***	**25.2 (22.5, 28.1)**	**27.7 (24.1, 30.4)**	**25.9 (23.3, 28.7)**
eGFR (mL/min/1.73 m^2)	**40.5 (33.6, 43.7)***	**77.6 (63.2, 89.9)**	**35.5 (28.8, 41.5)**	**71.8 (60.1, 85.6)**
Serum creatinine (μmol/L)	**132.6 (114.9, 159.1)***	**79.6 (69.8, 94.6)**	**142.8 (123.8, 176.8)**	**85.7 (70.7, 97.2)**
ACR (mg/mmol)	**2.1 (0.9, 6.5)***	**1.2 (0.7, 2.4)**	**3.6 (1.5, 14.3)**	**1.4 (0.8, 4.0)**
CRP (mg/L)	1.0 (0.6, 1.8)	0.7 (0.2, 1.7)	0.8 (0.3, 2.7)	0.7 (0.2, 1.7)
Systolic blood pressure (mmHg)	130 (119, 148)	132 (120, 146)	127 (120, 148)	128 (120, 140)
Diastolic blood pressure (mmHg)	**60 (58, 68)***	**65 (58, 70)**	**62 (58, 69)**	**62 (58, 68)**
Detectable C-peptide	**56.7***	**37.0**	**28.6**	**32.1**
Responder to MMTT	22.2	5.8	5.6	5.9
CVD	**34.5***	**28.8**	**68.2**	**42.8**
Neuropathy (MNSI ≥2)	73.3	68.8	73.9	74.3
Antihypertensive medication	**72.4***	**60.1**	**90.8**	**65.7**
Lipid-lowering medication	75.0	66.3	80.3	72.3
Exercise	**65.5***	**84.3**	**72.3**	**79.8**
Smoking	0	1.6	2.2	3.6
IA2	30.0	24.0	15.9	20.6
GAD65	26.7	28.5	31.8	27.0
DR3 or DR4	100.0	93.8	93.8	93.9

Data are median (IQR) or %. For C-peptide response to mixed-meal tolerance test (MMTT), *n* = 439. MNSI, Michigan Neuropathy Screening Instrument. *$P < 0.05$ between all groups. Boldface text highlights the differences between groups (equals *$P < 0.05$ between all groups).

CKD compared with those without CKD. In addition, HDL cholesterol was lower ($P < 0.001$) and the prevalence of exercise lower ($P < 0.001$) in those with CKD compared with those without. Interestingly, the highest prevalence of random detectable C-peptide was observed in the +CKD/−PDR group (56.7%) compared with the other groups (−CKD/−PDR 37.0%, +CKD/+PDR 28.6%, and −CKD/+PDR 32.1%; $P < 0.001$) (Table 1).

Medalists in the +CKD/−PDR group had lower prevalence of CVD (34.5%) than those with +CKD/+PDR and −CKD/+PDR (at 68.2% and 42.8%, respectively) ($P < 0.001$), with the lowest prevalence observed in the −CKD/−PDR group (28.8%) (Fig. 1 and Table 1). CKD alone without PDR was not associated with CVD (34.5% for +CKD/−PDR vs. 28.8% for −CKD/−PDR, $P = 0.51$).

FinnDiane Patients

From FinnDiane, only individuals with complete data on complications and a type 1 diabetes duration ≥25 years were included to ensure adequate time for development of micro- and macrovascular complications ($n = 675$) (Supplementary Table 2). Females comprised 45.2% of the cohort with median age of 44.9 years (IQR 38.9, 50.1) and diabetes duration of 32.7 years (28.6, 37.0). The prevalence of CKD was 28.3%, PDR 63.1%, and CVD 18.1% ($n = 675$) (Supplementary Table 2).

Analysis of the FinnDiane cohort showed a more severe metabolic profile including significantly higher weight-adjusted insulin doses (median 0.63 units/kg [IQR 0.51, 0.77] vs. 0.43 units/kg [0.34, 0.54]), HbA_{1c} (67 mmol/mol [59, 75] vs. 54 mmol/mol [49, 61]), total cholesterol (5.1 mmol/L [4.5, 5.8] vs. 4.1 mmol/L [3.6, 4.7]), LDL cholesterol (3.3 mmol/L [2.7, 3.8] vs. 2.0 mmol/L [1.7, 2.4]), and systolic (140 mmHg [128, 155] vs. 130 mmHg [120, 142]) and diastolic (80 mmHg [74, 88] vs. 64 mmHg [58, 70]) blood pressures compared with the Medalists. Use of lipid-lowering medication (22.8% vs. 70.3%) was lower, but the proportion of patients using antihypertensives did not differ between the Medalists (66.0%) and FinnDiane cohort (68.7%).

Comparisons were made using the same four categories as in the Medalist study: +CKD/−PDR ($n = 21$), −CKD/−PDR ($n = 228$), +CKD/+PDR ($n = 170$), and −CKD/+PDR ($n = 256$) (Fig. 1 and Table 2). Confirming the findings in the Medalists, the CVD prevalence in the +CKD/−PDR group was half that in the +CKD/+PDR group in the FinnDiane cohort yet did not reach statistical significance, likely due to small sample size and number of events: +CKD/−PDR 19.1% vs. +CKD/+PDR 37.1% ($P = 0.10$). The lowest CVD prevalence was observed in the −CKD/−PDR group (6.6%), whereas the prevalence in the −CKD/+PDR group was 15.1%.

Comparisons of Traits in Medalist Patients With CKD by PDR Status

Since the CVD prevalence in the +CKD/−PDR group was only half of that of the +CKD/+PDR group (34.5% vs. 68.2%, $P = 0.002$) (Fig. 1 and Supplementary Table 3), we further examined the effect of covariates between these two groups.

The patients in the +CKD/−PDR group were older at diagnosis of type 1 diabetes (median age 15 years [IQR 10, 21] vs. 10 years [7, 14], $P = 0.003$) and at study participation (73 years [67, 77] vs. 65 [62, 71], $P = 0.001$) compared with the +CKD/+PDR group (Supplementary Table 3). No differences were observed in sex or duration of diabetes. Moreover, no differences were seen in metabolic variables including daily weight-adjusted insulin dose, HbA_{1c}, total cholesterol, HDL cholesterol, triglycerides, or BMI. Also, differences were not observed in the renal markers eGFR or ACR. No differences were observed in systolic or diastolic blood pressures, although the +CKD/−PDR group had a lower proportion using antihypertensive medications compared with the +CKD/+PDR group (72.4% vs. 90.8%, $P = 0.028$). However, the +CKD/−PDR group also had a higher proportion of random detectable C-peptide (56.7%) compared with +CKD/+PDR group (28.6%, $P = 0.006$). No differences were observed between the groups in the proportion on lipid-lowering medication, reported moderate exercise, peripheral neuropathy, or smoking (Supplementary Table 3). The differences in the age at diagnosis between +CKD/−PDR and +CKD/+PDR were not independently associated with CVD in multivariable logistic regression models.

Comparisons of Traits in FinnDiane Patients With CKD by PDR Status

In contrast to the Medalists, there were nonsignificant differences in age at diagnosis of type 1 diabetes (median 12 years [IQR 8, 18] vs. 10 years [6, 15], $P = 0.47$) and at study participation (45 years [40, 53] vs. 44 years [39, 50], $P = 0.24$) between +CKD/−PDR and +CKD/+PDR groups (Supplementary Table 3). The

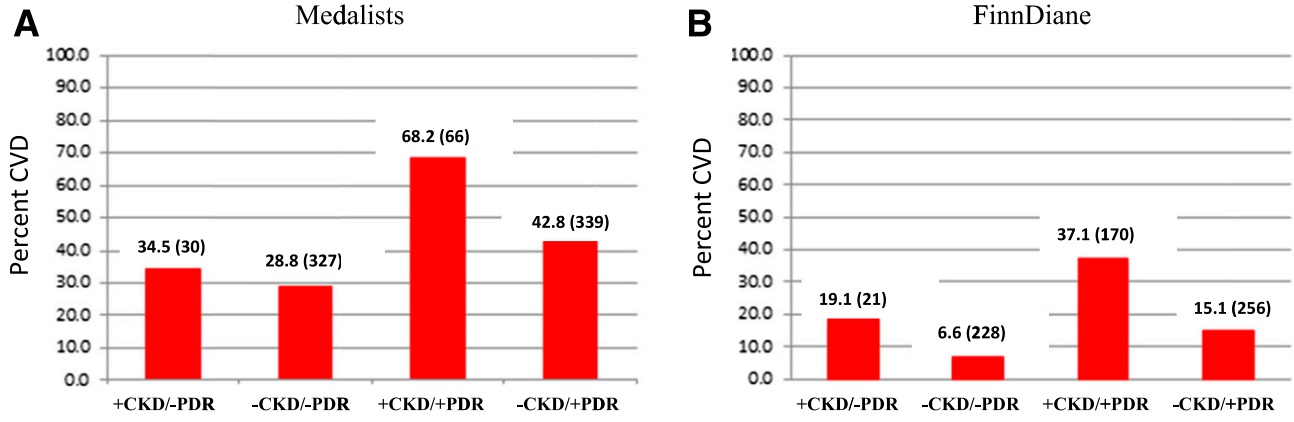

Figure 1—Differences in CVD prevalence across patients with and without CKD and PDR. Data are % (n per group) in Medalist patients (*A*) and FinnDiane patients (*B*). Overall $P < 0.001$ in both cohorts.

Table 2—Clinical characteristics of FinnDiane patients stratified by the presence of CKD and PDR

	+CKD/−PDR	−CKD/−PDR	+CKD/+PDR	−CKD/+PDR
N	21	228	170	256
Sex (male)	57.1	48.3	62.9	55.1
Age (years)	48.4 (40.2, 53.0)	45.2 (39.4, 51.1)	44.0 (39.2, 49.7)	45.6 (38.3, 50.7)
Age at diagnosis (years)	**12.1 (7.5, 18.3)***	**12.1 (6.9, 17.5)**	**10.4 (6.1, 15.4)**	**9.5 (5.5, 14.2)**
Duration (years)	33.9 (27.3, 36.2)	31.5 (28.3, 36.2)	32.9 (28.9, 36.9)	33.2 (28.6, 39.3)
Daily insulin dose (units/kg)	0.5 (0.43, 0.78)	0.61 (0.51, 0.73)	0.67 (0.53, 0.84)	0.63 (0.52, 0.77)
HbA_{1c} (%)	**7.8 (7.3, 8.6)***	**8.0 (7.4, 8.7)**	**8.4 (7.5, 9.2)**	**8.4 (7.8, 9.3)**
HbA_{1c} (mmol/mol)	**62 (56, 71)***	**64 (57, 72)**	**68 (58, 77)**	**68 (62, 78)**
Total cholesterol (mmol/L)	**5.2 (4.5, 5.8)***	**5.0 (4.4, 5.6)**	**5.3 (4.7, 6.2)**	**5.0 (4.4, 5.7)**
LDL cholesterol (mmol/L)	3.3 (3.0, 4.3)	3.2 (2.6, 3.7)	3.4 (2.8, 4.1)	3.2 (2.7, 3.8)
HDL cholesterol (mmol/L)	**1.0 (0.9, 1.5)***	**1.3 (1.1, 1.6)**	**1.1 (0.9, 1.4)**	**1.3 (1.1, 1.4)**
Triglycerides (mmol/L)	**1.32 (1.14, 1.67)***	**0.93 (0.72, 1.36)**	**1.59 (1.16, 2.39)**	**1.09 (0.85, 1.48)**
BMI (kg/m^2)	**24.2 (22.0, 25.9)***	**24.6 (22.7, 27.3)**	**24.7 (22.3, 27.5)**	**25.6 (23.3, 28.2)**
eGFR ($mL/min/1.73\ m^2$)	**40.8 (21.7, 44.1)***	**86.9 (75.4, 100.2)**	**33.3 (16.2, 43.7)**	**77.6 (63.0, 94.2)**
Serum creatinine (μmol/L)	**151.0 (123.3, 231.2)***	**79.3 (70.2, 91.7)**	**188.2 (120.4, 332.5)**	**88.9 (79.3, 104.2)**
ACR (mg/mmol)	**3.0 (0.3, 9.8)***	**0.1 (0.1, 0.4)**	**3.3 (0.5, 13.5)**	**0.6 (0.1, 3.0)**
CRP (mg/L)	**3.3 (2.2, 5.7)***	**2.0 (1.2, 4.2)**	**2.5 (1.6, 6.2)**	**2.3 (1.4, 4.4)**
Systolic blood pressure (mmHg)	**149 (137, 165)***	**134 (126, 145)**	**151 (137, 168)**	**141 (128, 153)**
Diastolic blood pressure (mmHg)	**83 (78, 88)***	**80 (72, 86)**	**85 (78, 90)**	**80 (72, 88)**
Detectable C-peptide levels	23.5	10.0	13.9	10.6
CVD	**19.1***	**6.6**	**37.1**	**15.1**
Antihypertensive medication	**95.2***	**40.8**	**96.5**	**73.4**
Lipid-lowering medication	**38.1***	**12.7**	**38.2**	**20.3**
Exercise	66.7	69.8	57.7	62.1
Smoking	14.3	27.4	19.4	22.8

Data are median (IQR) or %. Exercise data available in 50% of the patients. Boldface text highlights the differences between groups (equals $*P < 0.05$ between all groups).

+CKD/−PDR group showed a trend toward a higher proportion of detectable C-peptide (23.5% vs. 13.9%, $P = 0.29$) compared with the +CKD/+PDR. The cardiovascular risk profile was associated with nonsignificantly worse HbA_{1c} (68 mmol/mol [59, 77] vs. 62 [56, 71]), but total cholesterol, HDL cholesterol, triglycerides, systolic or diastolic blood pressure, antihypertensive medication, and lipid-lowering treatment were not different between +CKD/+PDR and +CKD/−PDR groups. The daily weight-adjusted insulin dose was significantly higher in the +CKD/+PDR compared with the +CKD/−PDR group (Supplementary Table 3).

Medalist Patients With CKD With and Without Peripheral Diabetic Neuropathy

For determination of whether the increased prevalence of CVD among those with both CKD and PDR was related to an overall predisposition to microvascular complications or whether there was a specific relationship with PDR, the presence of neuropathy with CKD/PDR was determined. Indeed, no difference in CVD prevalence was observed between groups (59.5% for +CKD/+neuropathy vs. 55.2% for +CKD/−neuropathy, $P = 0.66$) (Supplementary Fig. 1). No significant difference in the prevalence of CVD was observed in patients with renal disease without PDR with or without neuropathy (39.1% for +CKD/−PDR/+neuropathy vs. 12.5% for +CKD/−PDR/−neuropathy, $P = 0.17$).

Multivariable Logistic Regression Analysis in Medalists

Multivariable logistic regression analyses were performed to examine potential confounders of the relationship between CVD presence and CKD/PDR status. +CKD/−PDR remained independently associated with CVD (odds ratio 0.21 [95% CI 0.08–0.58]; $P = 0.003$) (Supplementary Table 3) after adjustment for several factors as explained in RESEARCH DESIGN AND METHODS. Exercise was the only covariate that remained significant in the model (0.24 [0.08–0.70]; $P = 0.009$). As there were moderate differences in eGFR and ACR between the +CKD groups, they were tested in the model for effect modification and did not have significant effect (Supplementary Table 4).

Renal Histology and Retinal Parameters of Patients With CKD With and Without PDR in Medalists

A subset of Medalists had whole postmortem kidneys available for histologic characterization of diabetic nephropathy: +CKD/+PDR, $n = 8$, and +CKD/−PDR, $n = 4$ (Supplementary Table 5). Sections were prepared from across the kidney in a standardized fashion retrieving a median of 245 glomeruli (IQR 168, 289). Figure 2 shows images of renal tissue and seven standard fields of retina from a patient demonstrating differential microvascular protection after >65 years of type 1 diabetes.

No differences were found in the severity of DN between the two groups (+CKD/+PDR vs. +CKD/−PDR) (Supplementary Table 5) (18) on such parameters as glomerular basement membrane thickness, arteriolar hyalinization, or percentage of global glomerular sclerosis. One patient had a range of no signs to mild (class 0–IIa) signs of diabetic nephropathy

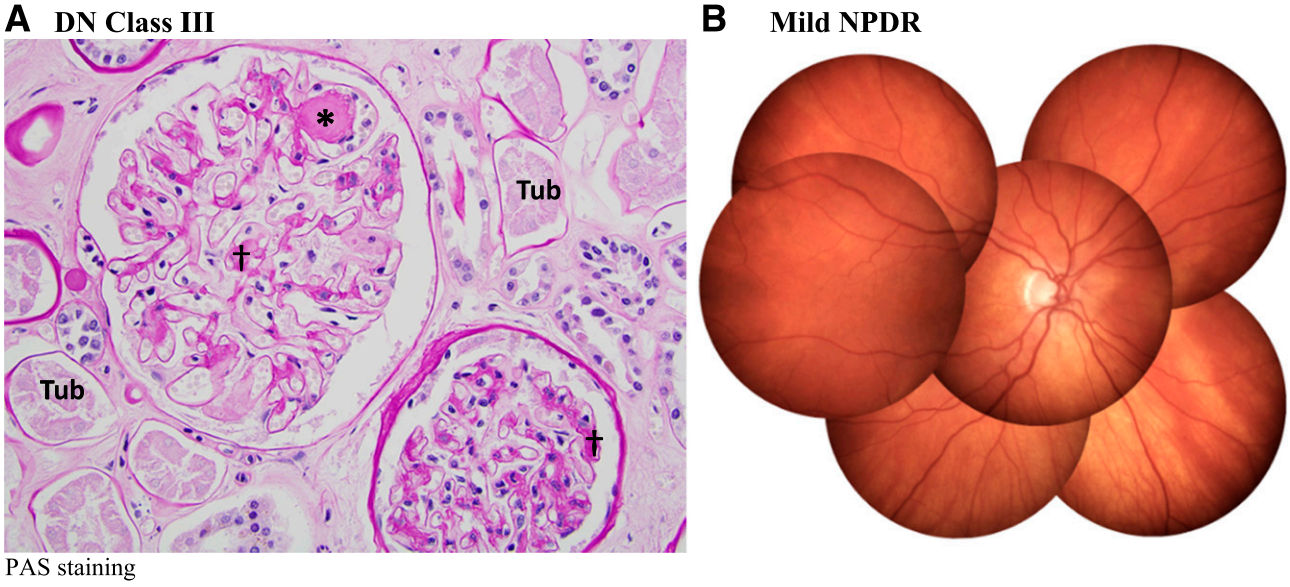

Figure 2—Kidney (*A*) and retinal (*B*) photographs of a 72-year old Medalist patient with 66 years of type 1 diabetes and severe diabetic nephropathy (DN class III), but only mild DR (nonproliferative DR [NPDR]), and no CVD, showing differential protection. PAS, periodic acid-Schiff staining; Tub, tubule. *Kimmelstiel-Wilson nodule. †Mesangial expansion.

in the specimen, whereas three patients had severe findings (class IIb–III) in the +CKD/−PDR group. In the +CKD/+PDR group, three patients showed class 0–IIa and five showed class IIb–III (P = 0.48). Non–diabetes-related pathologies such as glomerulonephritis or malignancies were not observed in the examined slides. Patients in the +CKD/+PDR group showed clear signs of PDR in retinal photos according to the diagnostic criteria for PDR. Those in the +CKD/−PDR group had only a range of no DR to mild DR as verified in retinal fundus photography graded per ETDRS standards.

CONCLUSIONS

The novel finding of our study is that the absence of PDR in those with stage 3b CKD is associated with a lower prevalence of CVD in patients with long duration of type 1 diabetes. This is further supported by validation in patients with shorter duration of type 1 diabetes (FinnDiane). These unexpected findings suggest that PDR adds to the toxicity of CKD in the development of CVD or that there could be a common protective factor against hyperglycemic toxicity for severe diabetic eye disease and CVD.

Many studies have documented that renal disease is a major contributor to the excess CVD and mortality of those with type 1 diabetes within the first 30 years of duration (5,6,24). However, the results of the Medalist study show that the development of CVD in the presence of stage 3b CKD is not inevitable, particularly in those without PDR. This trend was also observed in a cohort with type 1 diabetes with a duration <50 years (>25 years) in FinnDiane.

Some studies have reported that DR is associated with myocardial perfusion defects and poor coronary flow reserve (25–28). In the Atherosclerosis Risk in Communities (ARIC) study, fatal coronary artery disease events were threefold more common in patients with type 2 diabetes and any DR compared with those without DR even after relevant covariates (although not renal disease) were controlled for (29). Recently, a meta-analysis showed an association between diabetic macular edema and proliferative diabetic retinopathy with CVD again in type 2 diabetes (7). However, Klein et al. (10) in WESDR reported an increase in CVD mortality among patients with type 1 diabetes with visual impairment but did not observe an increase in mortality among those with diabetic macular edema or PDR. PDR correlated with all-cause mortality in FinnDiane and the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study but not independently from diabetic kidney disease (5,24). However, these studies could not directly determine the contribution of CKD to CVD independent of PDR, since most subjects with diabetes and renal disease have significant eye disease. In the Medalist study, the availability of individuals with diabetes and stage 3b CKD without PDR allowed the surprising finding that the presence of stage 3b CKD alone without PDR did not increase the risk of CVD in type 1 diabetes (Fig. 1). Similar patterns in both the Medalist study and FinnDiane of the prevalence of CVD being approximately half among those without PDR compared with those with PDR in the presence of CKD were found. This finding suggests that there may be common protective factors for PDR and CVD.

In the overall cohorts, as expected, diabetic renal disease showed a stronger association with CVD in patients with shorter diabetes duration compared with Medalists with extreme duration. As Medalists were older, this may indicate that Medalists with CKD have a less severe form of CKD, and the findings may be reflecting a survival effect of these individuals having been spared a more severe form of diabetic renal disease. Countering this possible bias, a similar trend toward protection from CVD in the absence of PDR is seen in the sample from FinnDiane of shorter duration. Indeed, this group has significant risk factors for complications including higher insulin doses, higher HbA_{1c}, and worse lipid profile. This suggests that the findings are unlikely to be driven by the "survivor" bias alone

or the better risk factor profile seen in the Medalists. Importantly, we are in the process of collecting prospective data to determine the concomitant development of CVD in patients with and without diabetic kidney disease and eye disease, respectively.

The findings that Medalists with kidney disease and without severe eye disease were older at diabetes diagnosis than those with both microvascular complications raised the question of whether hyperglycemia during puberty may have affected the relationship between the severity of DR and CVD. However, we did not observe any significant associations of indicator variables representing the temporal relationship of onset of diabetes to onset of puberty with CVD or significant interactions with the relationship of PDR in those with stage 3b CKD to CVD (data not shown). Thus, our results do not support the assumption that hyperglycemia during puberty would have had an effect on the main results. In contrast, FinnDiane reported a higher risk for PDR in patients with a diabetes debut before the age of 15 years compared with those diagnosed with diabetes at the age of 15 years or later (30).

Previously, we demonstrated the Medalist group to be potentially enriched with protective factors, since HbA_{1c} levels were not related to the prevalence of severe diabetic eye and kidney disease (31,32). Following on the idea of protection from hyperglycemic toxicity, we have reported that multiple enzymes in the glycolytic, aldose reductase, glyoxalase, and mitochondrial pathways were elevated in the glomeruli derived from Medalists, who were protected from diabetic nephropathy in spite of chronic hyperglycemia (33). Further, activation of pyruvate kinase M2, a key enzyme in glycolysis, reduced markers of renal dysfunction by elevating glycolytic flux and activating mitochondrial biogenesis and function in mouse models of diabetes. These data provide potential mechanisms for protection against diabetic kidney disease in the Medalists.

One potential explanation for patients with stage 3b CKD and PDR developing more CVD compared with those without severe eye disease is that their vascular pathologies are more severe, which suggests the presence of PDR is merely reflecting this tendency. Multiple lines of evidence suggest that this is unlikely. One is that the presence of neuropathy did not affect the risk for CVD. Second, there is no evidence of significantly more severe disease between the two groups, such as in eGFR or albuminuria between the CKD groups. This was demonstrated by the absence of confounding in multivariable models by these factors or those that may be related to both complications including antihypertensive use. Finally, the degree of histological severity of glomerular pathology did not differ between the CKD with and without PDR groups. Given that several previous studies show strong links among renal and retinal disease and CVD overall, these results raise a question regarding what common factor may protect the vessels of the eye and cardiovascular system but not the kidneys.

Multiple possible factors could be involved in this differential protection for the retinal, renal, and cardiovascular tissue in diabetes. Of particular interest could be insulin and vascular endothelial growth factor (VEGF), which have been targets of therapeutic modulations for all three complications (34–36). Interestingly, VEGF expressions are elevated in the retina and renal glomeruli yet decreased by diabetes in the myocardium. This differential tissue expression of VEGF in diabetes has made systemic treatments targeting VEGF difficult but may provide an explanation for differential contributions to CKD, PDR, and neuropathy in addition to CVD (31).

Another common pathway is the role of insulin or insulin resistance, which has been reported to affect the progression of diabetic nephropathy, DR, and CVD in diabetes. Among Medalists, the finding that a greater proportion of patients with CKD who were protected from PDR and CVD had detectable C-peptide levels is interesting. Whether preserving β-cell function can lower risk for CVD in patients with CKD is an intriguing question and needs further study (37).

Due to the potential survival bias, it is important to confirm these findings in patients with shorter duration of type 1 diabetes in order to determine generalizability of the findings. Therefore, the analysis was replicated in FinnDiane, a multicenter longitudinal study of those with shorter duration of type 1 diabetes. Indeed, the findings were similar in both cohorts, confirming that CVD prevalence in those without PDR was approximately half the prevalence in those with PDR despite the presence of CKD, supporting the idea that factors may exist that jointly protect those with type 1 diabetes from PDR and CVD. However, the limited sample size and number of patients with CVD in the longitudinal study likely prevented statistical significance. Differences in the clinical exams and laboratory tests between the two cohorts also need to be acknowledged. However, definitions for vascular complications were equally defined, and the marginal dissimilarity in the cutoff for PDR (ETDRS 53 vs. 60) was considered not relevant. Finally, the results did not change after adjustment for exercise, shown to be strongly associated with CVD in the Medalists (13).

These findings demonstrate an unexpectedly consistent pattern of a decreased prevalence of CVD among those with stage 3b CKD without PDR in those with type 1 diabetes after at least 25 years of type 1 diabetes. Further studies are warranted in order to investigate whether the presence of both PDR and CKD is a marker of more generalized vascular dysfunction or whether tissue-specific protective factors are in play.

Acknowledgments. The Medalist study received, and the authors gratefully acknowledge, assistance from the Clinical Research Center. The FinnDiane physicians and nurses at each participating center are gratefully acknowledged for help with patient recruitment and collection of samples and data (Supplementary Table 6). The authors thank Suzanne Bergenhenegouwen for the technical assistance with the retinal photo.

Funding. The Joslin 50-Year Medalist study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (P30-DK-036836, UL1-RR-025758-03, R24-283-DK-083957-01, DP3-DK-094333-01, and T32-DK-007260), JDRF (17-2013-310), Tom Beatson Foundation, Jr 284 Foundation, and many Medalists. This work was supported in part by the Mary K. Iacocca Fellowship provided by the Iacocca Family Foundation. This study was also supported by grants from the Folkhälsan Research Foundation; Wilhelm and Else Stockmann Foundation; Liv och Hälsa Foundation; Medical Society of Finland (Finska Läkaresällskapet); Finnish Medical Foundation; Swedish Cultural Foundation in Finland; Biomedicum Helsinki Foundation; Dorothea Olivia, Karl Walter och Jarl Walter Perkléns Foundation; Academy of Finland; Novo Nordisk Foundation; and Päivikki and Sakari Sohlberg Foundation and was supported by EVO governmental grants.

Duality of Interest. P.-H.G. has received investigator-initiated research grants from Eli Lilly and Roche, is an advisory board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, Merck Sharp & Dohme (MSD), Novartis, and Sanofi; and has received lecture honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly,

Genzyme, MSD, Novartis, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.G. and H.A.K. researched data, performed statistical analyses, and wrote the manuscript. V.H. and L.T. researched data, performed statistical analyses, and contributed to the manuscript. P.S.A. and I.E.S. assessed all the human kidney pathology. W.F., J.K.S., C.F., D.P., S.D., M.K., and P.-H.G. contributed to discussion and reviewed and edited the manuscript. G.L.K. researched data and wrote the manuscript. All the authors reviewed the manuscript. G.L.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 4th Banting & Best Diabetes Centre/Joslin Diabetes Center/University of Copenhagen Conference, Toronto, Ontario, 20–21 October 2017, and the 51st European Association for the Study of Diabetes Meeting, Stockholm, Sweden, 14–18 September 2015.

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